U.S. FOOD & DRUG ADMINISTRATION

Registration & Listing Compliance Program

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Tasneem Hussain Pharm. D

Learning Objectives

- Discuss the differences between two types of submission errors
- Discuss our registration and listing compliance program
- Discuss the common registration and listing data errors with examples
- Discuss how to address submission errors to get open cases resolved

Submission Errors

- Automated validation errors - before an electronic submission is accepted
  - System generated
    - Firm is notified by CDER Direct through an email to check the status of the submission
- Compliance review errors – after an electronic submission is accepted
  - Manual review of the data through surveillance projects
  - Submission errors sent through deficiency letters

Our Compliance Program

Established in Fall of 2015

Our Mission: To achieve accuracy and integrity of establishment registration and drug listing data

Four phases:

- Surveillance
- Deficiency letter
- Data removal
- Untitled Letter or Warning Letter

Audience Poll Question 1

Which one of these is a compliance review error?

A. ID (registrant's DUNS Number) must not be associated with any other set id of document type "Establishment registration”

B. If the NDC product/item code was previously submitted, then the product name is same as in the most recent submission for this NDC product/item code

C. Blanket No Changes Certification of Product Listing" documents must be submitted during the time frame of October 1st through December 31st each year.

D. The NDC in the listing SPL does not match the NDC on the carton label

Top Establishment Registration Compliance Errors

- Manufacturing establishment is not currently registered but engaged in manufacturing processes
- Non drug manufacturers registered with FDA
  - PLDs or Importers
- Outdated establishment address or contact info
- Missing US agent or importer information
- Incorrect business operations

Top Drug Listing Compliance Errors

- Strength
  - Incorrect calculation or conversion from (%) to w/w or w/v etc.
  - Incorrect presentation in the listing SPL
  - Missing or incorrect units of measure

- NDC
  - Mismatch in labeling and SPL
  - Source NDC used in labeling (carton label and/ or How Supplied section)
  - Discontinued NDC used in labeling

Top Drug Listing Compliance Errors

- Active ingredients
  - Incorrect or mismatched list of active ingredients in labeling and listing SPL
- Labeling
  - Incorrect carton label
    - Image belongs to a different drug
    - Image is of a different strength of drug

Top Drug Listing Compliance Errors

- Proprietary name
- Route of administration
- Dosage form
- Packaging information
- Application number

Top Drug Listing Compliance Errors

Drug listing submissions that utilize a type of reference listing file

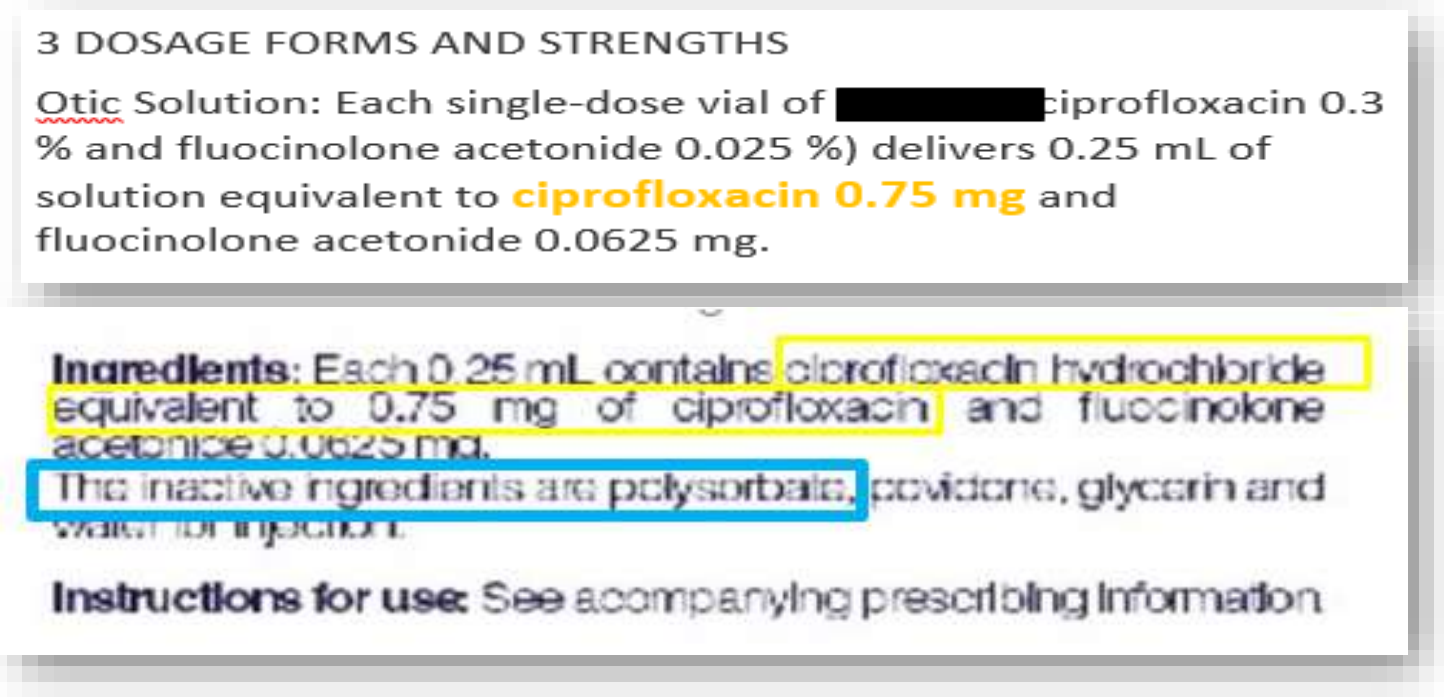
- The NDA product or the reference listed drug (RLD) used by generic drug manufacturers includes incorrect data
- Source drug listing used by repackagers includes incorrect data
- Repackagers and generic manufacturers should verify the data before using it to submit their own listings

Other issues:

- Repackager's listing submission must include the repackager's NDC on all labeling (How Supplied Section, carton label)
- Source drug cited should be actively listed

Drug Listing Errors Ex. 1

Incorrect strength and incorrect active ingredient– Images from the package insert and carton label



3 DOSAGE FORMS AND STRENGTHS

Otic Solution: Each single-dose vial of [redacted]ciprofloxacin 0.3 % and fluocinolone acetonide 0.025 %) delivers 0.25 mL of solution equivalent to **ciprofloxacin 0.75 mg** and fluocinolone acetonide 0.0625 mg.

Ingredients: Each 0.25 mL contains ciprofloxacin hydrochloride equivalent to 0.75 mg of ciprofloxacin and fluocinolone acetonide 0.0625 mg.

The inactive ingredients are polysorbate, povidone, glycerin and water for injection.

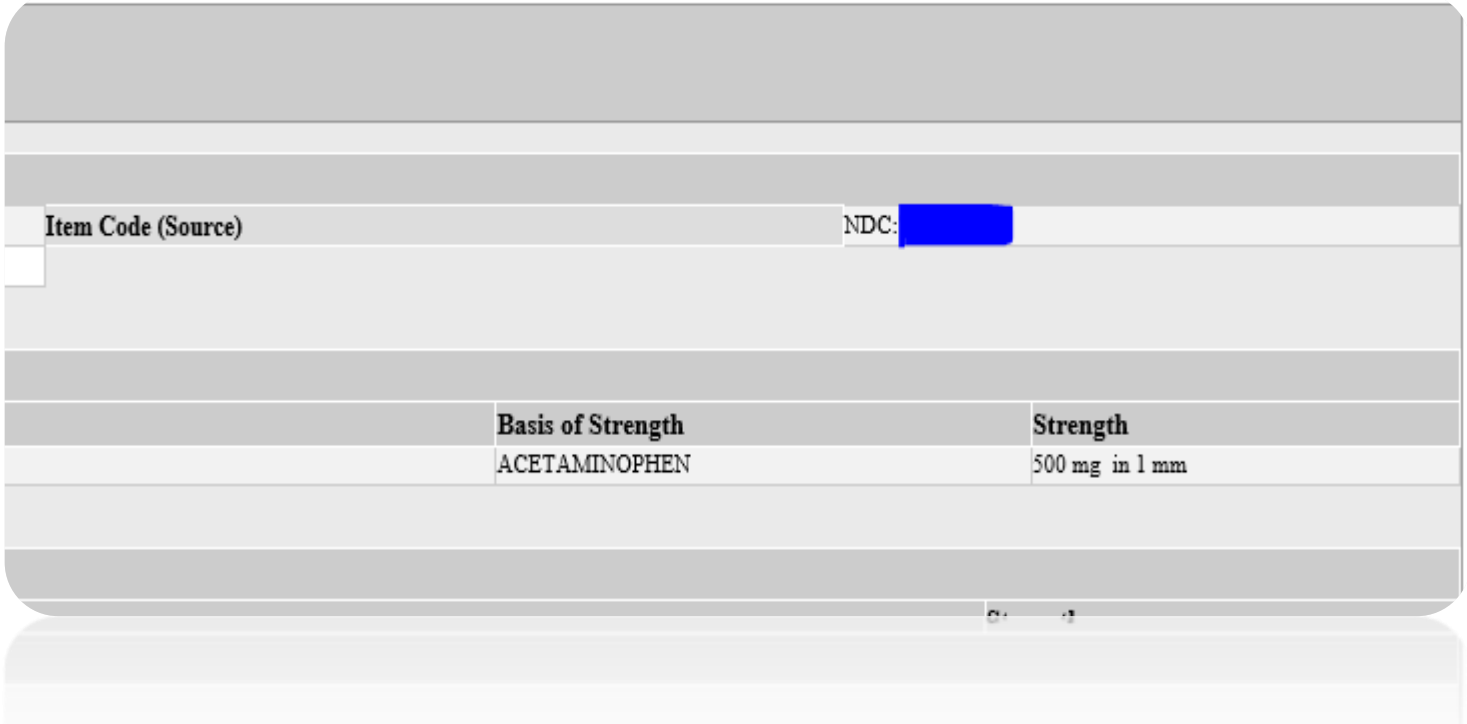
Instructions for use: See accompanying prescribing information

Drug Listing Errors Ex. 1

Basis of Strength	Strength
CIPROFLOXACIN	872.5 ug in 0.25 mL
FLUOCINOLONE ACETONIDE	62.5 ug in 0.25 mL
Polysorbate 80	6250 ug in 0.25 mL

Drug Listing Errors Ex. 2

- Incorrect strength



Item Code (Source)	NDC: [redacted]	
	Basis of Strength	**Strength**
	ACETAMINOPHEN	500 mg in 1 mm

Drug Listing Errors Ex. 2

Score	no score
Size	12mm
Imprint Code	PARA500

Packaging

#Item Code	Package Description
1 NDC:	16 mm in 1 BLISTER PACK; Type 0: Not a Combination Product

Drug Listing Errors Ex. 3

- Incorrect carton label

Drug Listing Errors Ex. 3

Item Code (Source)	NDC: [redacted]
DEA Schedule	CII

	Basis of Strength	Strength
	HYDROCODONE BITARTRATE	10 mg
	ACETAMINOPHEN	500 mg

Audience Poll Question 2

How would you convert the strength of Hydrocortisone ointment with a concentration of 2.5% into w/w presentation to list in the SPL strength field?

A. 2.5g/2.5g

B. 0.025mg/100g

C. 25mg/1g

D. 25g/30g

Explanation of Poll Question 2

- 2.5% is equal to 2.5 grams in 100 gm and we want to list using a w/w ratio with the units mg / g
- 2.5 g = 2,500 mg and this is equal to the ratio of 2,500 mg to 100 g
- But then when we want to express the amount of Hydrocortisone in 1 g, that would be 25 mg of Hydrocortisone in 1 g of the base
- Thus under the strength data element field of the SPL, for the numerator you would enter 25 for the strength and you would enter “mg” for the unit of measure
- For the denominator you would enter 1 as the strength and you would enter “g” for the unit of measure
- The package size would be listed as 30 g under the package description section of the SPL

Strength Conversion Chart

- https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/strength-conversion-drug-listing

Product	Numerator unit	Denominator unit
Alcohol, Medical Gasses, Water	Volume	Volume
Oral Solid	Weight	Each
Oral Liquid	Weight	Volume
Oral powder for reconstitution with a known volume	Weight	Volume
Oral powder for reconstitution with a variable volume	Weight	Each
Suppository	Weight	Each
Injection Liquid	Weight	Volume
Injection powder for reconstitution with a known volume	Weight	Volume
Injection powder for reconstitution with a variable volume	Weight	Each
Inhaler powder	Weight	Each
Inhaler liquid	Volume	Each
	Weight	Volume
Inhaler blister	Weight	Each
Topical cream or ointment	Weight	Weight
Topical gel	Weight	Volume
	Weight	Weight
Topical lotion	Weight	Volume
Transdermal patch	Weight	Time
	Weight	Weight
	Weight	Each
Topical patch	Weight	Weight
	Weight	Each
Bulk liquid	Weight	Volume
Bulk solid	Weight	Weight

Facts and Myths

- Contract manufacturers must list all drugs they manufacture using their own NDC and labeler code
  - Fact

- Private Label Distributors are required to register with FDA
  - Myth

Facts and Myths

- Contract Manufacture listings do not require the submission of the package insert
  - Fact

- Contract manufacturers' drug listings get published in DailyMed
  - Myth

Resolving Open Compliance Cases

Manual overrides

If you receive system generated validation errors as a result of correcting a deficiency

- Email our office with a list of the error(s) and the Core-ID of the failed submission
- We will review and contact you
  - To make further changes if needed
  - Once we approve the manual override, contact SPL@fda.hhs.gov with the approval
  - Once your override request is submitted or approved, don't change anything with that submission
  - Manual overrides will only be granted for corrections to the specific error(s) that we have identified and not necessarily for other errors you may generate during your updating process

Resolving Open Compliance Cases

- Compliance cases will not be closed and data will not go back into the online directories until ***all*** errors are addressed and corrected

- A new listing version will not automatically extend your certification date until the compliance case is closed

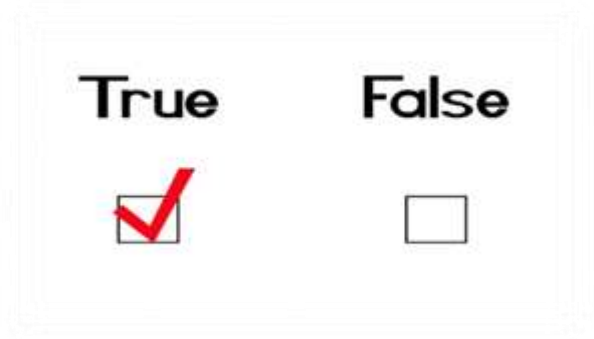
- When a listing SPL is associated with an open compliance case --cannot use a “Blanket No Change Certification SPL” to certify your listing

Challenge Question 1

A firm gets inspected by FDA and the officers find that there are no products manufactured there

– This firm may be a Private Label Distributor-

- True or False?
- Answer is True



Challenge Question 2

How do you express the strength of alcohol in a listing SPL?

- a. w/w
- b. w/v
- c. v/v
- d. v/w
- Answer: c

Online Resources

- Online webpage:
  - Updated periodically
  - Includes helpful resources and links
  - Includes list of all published R&L WLs to date

https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/electronic-registration-and-listing-compliance-program

- cderdirect@fda.hhs.gov

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Thank You

Tasneem.Hussain@fda.hhs.gov

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Compliance Case Studies

Julian Chun, PharmD, MBA, BCACP
Pharmacist
Drug Registration and Listing Staff
CDER | US FDA

Learning Objectives

- Troubleshoot establishment registration and drug listing issues
- Identify and fix validation errors in submitted SPLs

Case Studies

- Divide into three groups
- Each group will have 10 minutes to discuss the case and submit a correction
  - https://direct.preprod.fda.gov
- Reconvene and discuss cases and solutions

Group 1

- Your product is detained at the border
- Customs states your contract manufacturer has not listed your drug, though you have an NDC
- Where do you check to verify listing status?
  - What are you checking?

Group 1 – Case Details

- Your drug: Wonderdrug tablets
- Your NDC: 55555-555-01
- Your contract manufacturer: Placebo Pharma
  - Labeler code: 12345
- Username: fda_group_1 / Password: FDA#1234

Group 2

- You receive a deficiency letter that states your strength is incorrect
- How do you express strength in SPL?
- What steps do you take to resolve the deficiency?

Group 2 – Case Details

- Deficiency Letter
- Strength conversion
  - https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/strength-conversion-drug-listing
- Username: fda_group_2 / Password: FDA#1234

Group 3

- You try to certify your drug, but it fails due to an establishment that has an expired registration
- What steps do you take to resolve the validation?

Group 3 – Case Details

- Establishment: Wonder Pharma
  - DUNS: 987654321
- Username: fda_group_3
  - Password: FDA#1234

Group 1 – Answers

- Listing status can be check on NDC Directory
  - https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory
- Items removed from the Directory are marked in red
  - (E) = compliance initiated

Group 1 – Answers

- Clone submitted SPL in CDER Direct and generate new set ID
- Make sure to remove references to other NDCs (black out or super-impose your NDC)
- Full content of labeling is not required for drugs manufactured under contract

Group 2 – Answers

- Strength must be represented as a ratio (i.e., w/w or w/v)
  - 2% = 2g/100g → 2000mg/100g → 20mg/1g
    - 2% = 2mg/100mg. Will this pass validation?
  - Liquid: 2% = 2g/100ml → 2000mg/100ml → 20mg/ml

Group 2 – Answers

- Changes to strength are only allowed when fixing an initial error
  - Any other strength changes require a new NDC
- Send core ID / submission ID (begins with a “c”) to compliance officer for review
  - Compliance officer will approve for manual override or request additional changes

Group 3 – Answers

- No Changes Certification will only work if no changes are necessary
- Must send an updated submission since SPL contains an expired establishment

Questions

Compliance questions: edrls@fda.hhs.gov

Technical questions: cderdirect@fda.hhs.gov


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